

We claim:

1. A method for improving learning or memory in a subject, which comprises modifying NMDA receptors in neural synapses of the subject's brain, such that NMDA receptor function is increased by at least 15% as compared with an equivalent unmodified subject, the modification resulting in improved learning or memory in the subject.
2. The method of claim 1, comprising modulating NMDA receptor function in the subject's brain with a chemical compound.
3. The method of claim 1, comprising increasing a ratio of NR2B to NR2A subunits in the NMDA receptors of the subject's brain.
4. The method of claim 3, comprising treating the subject to increase production or decrease degradation of NR2B receptor subunits in the subject's brain, resulting in an elevated amount of NR2B subunit as compared with the amount produced by an equivalent, but untreated subject.
5. The method of claim 4, wherein the treatment results in the presence of at least twenty percent more NR2B subunit in the treated subject, as compared with an equivalent, but untreated, subject.
6. The method of claim 4, wherein the treating comprises genetically altering the subject with an exogenous nucleic acid molecule that encodes NR2B, constructed so as to produce NR2B in the brain of the subject.

10009228 "031203
20220908 08220007

7. The method of claim 6, wherein the genetic alteration is inheritable.

5 8. The method of claim 6, wherein the genetic alteration is not inheritable.

9. The method of claim 1, wherein the subject is an adult.

10

10. The method of claim 1, wherein the subject is a juvenile.

11. The method of claim 7, wherein the subject
15 is an embryo.

12. The method of claim 1, wherein the subject is a mammal.

13. The method of claim 12, wherein the mammal
20 is a mouse.

14. The method of claim 12, wherein the mammal is a human.

25

15. A method of treating a neurodegenerative disorder affecting learning or memory in a patient in need of such treatment, which comprises modifying NMDA receptors in neural synapses of the patient's brain, such
30 that the NMDA receptor function is increased by at least 15% as compared with an equivalent unmodified patient, the modification resulting in improved learning or memory in the patient.

35

1009228.034203
2021082260001

16. The method of claim 15, comprising enhancing NMDA receptor function in the brain with a chemical compound.

5 17. The method of claim 15, comprising increasing a ratio of NR2B-containing NMDA receptors to NR2A-containing NMDA receptors in the patient's brain.

10 18. The method of claim 17, comprising stimulating production or inhibiting degradation of NR2B receptor subunits in the patient's brain, resulting in an increased amount of NR2B subunit as compared with the amount produced by an equivalent, but untreated patient.

15 19. The method of claim 18, wherein the treatment results in at least twenty percent more NR2B subunit than found in an equivalent, but untreated patient.

20 20. The method of claim 18, wherein the stimulation of production of NR2B subunits is accomplished by genetically altering the patient with an exogenous nucleic acid molecule that encodes NR2B, constructed so as to produce NR2B in the brain of the
25 patient.

21. The method of claim 15, wherein the patient is an adult.

30 22. The method of claim 15, wherein the patient is a juvenile.

23. A genetically altered non-human animal having enhanced synaptic plasticity and improved learning
35 and memory as compared with an equivalent, but unaltered

10009228 "031E03

animal, the genetic alteration resulting in a modification of NMDA receptors in neural synapses of the patient's brain, such that the NMDA receptor function is increased by at least 15% as compared with an equivalent
5 unaltered animal.

24. The genetically modified animal of claim 23, wherein the animal over-expresses an endogenous gene encoding NR2B.

25. The genetically modified animal of claim 23, wherein the animal expresses a transgene encoding NR2B.

26. The transgenic animal of claim 23, selected from the group consisting of mouse, rat, cat, dog, dolphin and non-human primate.

27. The transgenic animal of claim 23, wherein the genetic alteration is inheritable.

28. A method of identifying compounds that enhance learning and memory in a subject by increasing expression of NR2B genes in the subject, which comprises providing a chimeric DNA construct comprising an NR2B promoter operably linked to a reporter gene, contacting the chimeric DNA construct with a test compound suspected of up-regulating the NR2B promoter, and measuring expression of the reporter gene, an increase in the expression being indicative that the test compound enhances learning and memory in the subject by increasing expression of NR2B genes in the subject.

29. An method for identifying compounds that enhance learning and memory in a subject by affecting

expression of NR2B or activity of NMDA receptors, which comprises:

- a) providing a pair of equivalent cells, one being transgenic and expressing an exogenous nucleic acid molecule encoding NR2B, and the other being non-transgenic for expression of an exogenous nucleic acid molecule encoding NR2B;
- b) treating the non-transgenic cell with a test compound suspected to affect the expression NR2B or activity of the NMDA receptors;
- c) comparing NMDA receptor function of the treated, non-transgenic cell with NMDA receptor function of the transgenic cell and, optionally, NMDA receptor function of an untreated, non-transgenic cell, a change in NMDA receptor function in the treated, non-transgenic cell that comprises the same features of NMDA receptor function exhibited in the transgenic cell being indicative that the test compound enhances learning and memory in a subject by affecting expression of NR2B or activity of NMDA receptors.

30. The method of claim 29, wherein the cells are disposed within a tissue.

31. The method of claim 30, wherein the tissue is disposed within a living animal.

32. The method of claim 30, wherein the NMDA receptor function is measured electrophysiologically.

33. The method of claim 32, wherein the NMDA receptor function is measured by measuring peak amplitude or channel decay time of NMDA receptors.

- 50 -

34. The method of claim 31, wherein the NMDA receptor function is measured using behavioral tests of learning and memory.

5 35. An *in vivo* assay for identifying compounds that enhance function of NMDA receptors in a subject, which comprises:

- a) providing a pair of animals;
- b) treating one of the animals with a test
10 compound suspected of enhancing NMDA receptor function; and
- c) directly or indirectly measuring a change in NMDA function in the treated animal as compared with the untreated animal, a change being indicative that the test
15 compound affects NMDA receptor function in a subject.

36. The method of claim 35, wherein the animals are the genetically altered animals of claim 23.

20 37. The method of claim 35, wherein the NMDA receptor function is measured electrophysiologically.

38. The method of claim 35, wherein the NMDA receptor function is measured by measuring peak amplitude
25 or channel decay time of NMDA receptors.

39. The method of claim 35, wherein the NMDA receptor function is measured using behavioral tests of learning and memory.

30

40. An *in vitro* assay for identifying compounds that enhance function of NMDA receptors in a subject, which comprises:

- a) providing a pair of cells;
- 35 b) treating one of the cells with a test

10069228.0312002

- 51 -

compound suspected of enhancing NMDA receptor function;
and

5 c) directly or indirectly measuring a change in
NMDA function in the treated cell as compared with the
untreated cell, a change being indicative that the test
compound affects NMDA receptor function in a subject.

10 41. The method of claim 40, wherein the cells
are genetically altered so as to possess enhanced NMDA
receptor function as compared with equivalent, but
unaltered cells.

15 42. The method of claim 40, wherein the NMDA
receptor function is measured electrophysiologically.

43. The method of claim 42, wherein the NMDA
receptor function is measured by measuring peak amplitude
or channel decay time of NMDA receptors.

20 44. A method of identifying genes and gene
products that affect NMDA receptor-mediated learning and
memory in a subject, which comprises:

25 a) providing a pair of equivalent animals,
one being transgenic and expressing an exogenous nucleic
acid molecule encoding NR2B, and the other being non-
transgenic for expression of an exogenous nucleic acid
molecule encoding NR2B;

30 b) comparing profiles of gene expression
or protein modification in the transgenic and non-
transgenic animals;

c) isolating one or more genes or gene
products whose expression is altered or modified in the
transgenic animal; and

35 d) identifying the one or more genes or
gene products.

100928 "031202

45. A method of identifying genes and gene products that affect NMDA receptor-mediated learning and memory in a subject, which comprises:

a) providing cells containing NMDA
5 receptors;

b) stimulating the NMDA receptors in a sample of the cells;

c) comparing profiles of gene expression or protein modification in the cell sample having stimulated NMDA receptors with an equivalent cell sample wherein the NMDA receptors are unstimulated;

d) isolating one or more genes or gene products whose expression is altered in the cells having stimulated NMDA receptors; and

15 d) identifying the one or more genes or gene products.

46. The method of claim 45, wherein the NMDA
receptors are stimulated by treatment with a chemical
20 compound.

47. The method of claim 45, wherein the NMDA receptors are stimulated electrically.

25 48. The method of claim 45, wherein the cells
are disposed within a tissue.

49. The method of claim 45, wherein the cells are disposed within a living organism.